

# UCSF

## UC San Francisco Previously Published Works

### Title

Basal parasympathetic deficits in C9orf72 hexanucleotide repeat expansion carriers relate to smaller frontoinsula and thalamus volume and lower empathy

### Permalink

<https://escholarship.org/uc/item/4426308v>

### Authors

Roy, Ashlin RK

Noohi, Fate

Morris, Nathaniel A

et al.

### Publication Date

2024

### DOI

10.1016/j.nicl.2024.103649

### Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at

<https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed



## Basal parasympathetic deficits in *C9orf72* hexanucleotide repeat expansion carriers relate to smaller frontoinsula and thalamus volume and lower empathy

Ashlin R. K. Roy<sup>a</sup>, Fate Noohi<sup>a</sup>, Nathaniel A. Morris<sup>a</sup>, Peter Ljubenkov<sup>a</sup>, Hilary Heuer<sup>a</sup>, Jamie Fong<sup>a</sup>, Matthew Hall<sup>a</sup>, Argentina Lario Lago<sup>a</sup>, Katherine P. Rankin<sup>a</sup>, Bruce L. Miller<sup>a</sup>, Adam L. Boxer<sup>a</sup>, Howard J. Rosen<sup>a</sup>, William W. Seeley<sup>a</sup>, David C. Perry<sup>a</sup>, Jennifer S. Yokoyama<sup>a</sup>, Suzee E. Lee<sup>a</sup>, Virginia E. Sturm<sup>a,b,\*</sup>

<sup>a</sup> Department of Neurology, University of California, San Francisco, CA 94158, USA

<sup>b</sup> Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA 94143, USA

### ARTICLE INFO

#### Keywords:

Autonomic nervous system  
Prosocial behavior  
Insula  
Behavioral variant frontotemporal dementia  
*C9orf72*

### ABSTRACT

Diminished basal parasympathetic nervous system activity is a feature of frontotemporal dementia that relates to left frontoinsula dysfunction and empathy impairment. Individuals with a pathogenic expansion of the hexanucleotide repeat in chromosome 9 open reading frame 72 (*C9orf72*), the most common genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis, provide a unique opportunity to examine whether parasympathetic activity is disrupted in genetic forms of frontotemporal dementia and to investigate when parasympathetic deficits manifest in the pathophysiological cascade. We measured baseline respiratory sinus arrhythmia, a parasympathetic measure of heart rate variability, over two minutes in a sample of 102 participants that included 19 asymptomatic expansion carriers ( $C9^+$  asymp), 14 expansion carriers with mild cognitive impairment ( $C9^+$  MCI), 16 symptomatic expansion carriers with frontotemporal dementia ( $C9^+$  FTD), and 53 expansion-negative healthy controls ( $C9^-$  HC) who also underwent structural magnetic resonance imaging. In follow-up analyses, we compared baseline respiratory sinus arrhythmia in the  $C9^+$  FTD group with an independent age-, sex-, and clinical severity-matched group of 26 people with sporadic behavioral variant frontotemporal dementia. The Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating-Sum of Boxes score was used to quantify behavioral symptom severity, and informant ratings on the Interpersonal Reactivity Index provided measures of participants' current emotional (empathic concern) and cognitive (perspective-taking) empathy. Results indicated that the  $C9^+$  FTD group had lower baseline respiratory sinus arrhythmia than the  $C9^+$  MCI,  $C9^+$  asymp, and  $C9^-$  HC groups, a deficit that was comparable to that of sporadic behavioral variant frontotemporal dementia. Linear regression analyses indicated that lower baseline respiratory sinus arrhythmia was associated with worse behavioral symptom severity and lower empathic concern and perspective-taking across the *C9orf72* expansion carrier clinical spectrum. Whole-brain voxel-based morphometry analyses in participants with *C9orf72* pathogenic expansions found that lower baseline respiratory sinus arrhythmia correlated with smaller gray matter volume in the left frontoinsula and bilateral thalamus, key structures that support parasympathetic function, and in the bilateral parietal lobes, occipital lobes, and cerebellum, regions that are also vulnerable in individuals with *C9orf72* expansions. This study provides novel evidence that basal parasympathetic functioning is diminished in FTD due to *C9orf72* expansions and suggests that baseline respiratory sinus arrhythmia may be a potential non-invasive biomarker that is sensitive to behavioral symptoms in the early stages of disease.

**Abbreviations:** UCSF, University of California, San Francisco; CDR, Clinical Dementia Rating Scale; VBM, voxel-based morphometry; RSA, Respiratory Sinus Arrhythmia, *C9orf72*, Chromosome 9 open reading frame 72.

\* Corresponding author at: UCSF Memory and Aging Center - Box 1207, Sandler Neurosciences Center, 675 Nelson Rising Lane, Suite 190, San Francisco, CA 94158, USA.

E-mail address: [virginia.sturm@ucsf.edu](mailto:virginia.sturm@ucsf.edu) (V.E. Sturm).

<https://doi.org/10.1016/j.nicl.2024.103649>

Received 26 February 2024; Received in revised form 16 July 2024; Accepted 29 July 2024

Available online 29 July 2024

2213-1582/© 2024 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Genetic forms of frontotemporal dementia (FTD) provide a critical window into the disease's earliest manifestations. Approximately 15–30 % of FTD cases are familial and caused by autosomal dominant mutations. (Greaves and Rohrer, 2019) The hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9orf72* or *C9*) is the most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS). (DeJesus-Hernandez et al., 2011; Gijssels et al., 2012; Ling et al., 2013) While in FTD there is predominant atrophy in the frontal and temporal lobes, in ALS there is progressive dysfunction in upper and lower motor neuron systems. Both FTD and ALS due to *C9orf72* expansions are associated with frontotemporal lobar degeneration with TAR DNA-binding protein 43 pathology (FTLD-TDP) and form two ends of a clinicoanatomical spectrum. People in families with *C9orf72* expansions, therefore, can present with either syndrome or exhibit mixed features of both. (Rohrer et al., 2015; Boeve et al., 2012) In some cases, dipeptide repeat protein inclusions and RNA foci may precede FTLD-TDP aggregation in *C9orf72* expansion carriers and create a preclinical window in which people lack overt symptoms but exhibit early signs of a disease process. (Lehmer et al., 2017; Gendron et al., 2017; Vatsavayai et al., 2019).

People with the pathogenic *C9orf72* expansion carry the genetic mutation from birth but typically do not develop symptoms until mid- to late-life. (Majounie et al., 2012; Gijssels et al., 2016; Moore et al., 2019) Although changes in language do not often arise in the clinical phase, alterations in emotions and social behavior are common. (Convery et al., 2019) Many *C9orf72* pathogenic expansion carriers develop the behavioral variant of FTD (bvFTD), (Sha et al., 2012; Solje et al., 2015) the most common clinical subtype of FTD, (Bang et al., 2015) which is characterized by loss of empathy, apathy, disinhibition, compulsivity, hyperorality, and executive dysfunction. (Rascovsky et al., 2011; Barker et al., March 10, 2022) The symptoms that emerge in *C9orf72* pathogenic expansion carriers with bvFTD resemble those of sporadic disease but more often include delusions and hallucinations. (Sha et al., 2012; Mahoney et al., 2012a; Devenney et al., 2014; Snowden et al., 2012; Kertesz et al., 2013) Anatomically, prominent atrophy and dysfunction in the frontoinsula (i.e., ventral anterior insula) and anterior cingulate cortex (Zhou et al., 2010; Pan et al., 2012; Rosen et al., 2002)—key hubs in the salience network (Seeley et al., 2007)—and in the frontal and temporal lobes more broadly are hallmark characteristics of bvFTD. (Rosen et al., 2002; Kril et al., 2005; Seeley et al., 2008) The neuroimaging features of bvFTD due to a *C9orf72* pathogenic expansion resemble those of sporadic cases but also often include atrophy in the medial pulvinar nucleus of the thalamus, parietal lobes, and cerebellum. (Rohrer et al., 2015; Sha et al., 2012; Mahoney et al., 2012a, b; Whitwell et al., 2012; Yokoyama and Rosen, 2012; Bonham et al., 2022; Bertrand et al., 2018; Lee et al., 2017; Bocchetta et al., 2020).

In bvFTD, salience network dysfunction relates to alterations in autonomic nervous system outflow. The salience network is a distributed neural system that guides behavior by triggering phasic bursts of autonomic and motor reactivity during emotions and by maintaining tonic physiological rhythms at rest. (Seeley et al., 2007; Sturm et al., 2018a; Guo et al., 2016b; Beissner et al., 2013) Laboratory-based studies have shown that people with bvFTD have diminished autonomic reactivity to stimuli that typically elicit negative emotions including disgust, embarrassment, and sadness, and these emotional reactivity deficits are associated with atrophy in salience network structures. (Sturm et al., 2013b; Sturm et al., 2006; Sturm et al., 2008; Scherling et al., 2017; Hua et al., 2019; Eckart et al., 2012; Verstaen et al., 2016; Muhtadie et al., 2019; Joshi et al., 2014; Marshall et al., 2019) Basal physiology (i.e., autonomic nervous system activity measured in task-free settings) is also impaired in bvFTD. Compared to healthy controls, people with bvFTD have lower baseline skin conductance levels, a sympathetic measure of eccrine sweat gland activity, and lower baseline respiratory sinus arrhythmia (RSA), a parasympathetic measure of vagally-mediated

heart rate variability. (Sturm et al., 2018a; Guo et al., 2016b; Joshi et al., 2014; Berntson et al., 1997; Sturm et al., 2018b) Lower baseline RSA in bvFTD relates to atrophy and lower functional connectivity in left-lateralized structures, including the left frontoinsula and anterior cingulate cortex, (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) structures that make important contributions to the dynamic control of the vagus nerve on the heart across the respiratory cycle. (Craig, 2005; Berntson et al., 1993).

Our previous studies have shown that diminished parasympathetic activity underlies some of the core socioemotional symptoms, such as loss of empathy, in bvFTD. (Sturm et al., 2018b) Empathy can come in several forms. Whereas emotional empathy (e.g., empathic concern) produces feeling states that are shared between people, cognitive empathy (e.g., perspective-taking) allows people to identify the thoughts and feelings of others. (Stellar et al., 2015; Beauchaine et al., 2013; Di Bello et al., 2020; Kogan et al., 2015; Miller et al., 2016; Porges, 2003; Porges, 2009; Oveis et al., 2009; Batson et al., 1995; Goetz et al., 2010) The parasympathetic nervous system encourages empathy and prosocial behaviors, such as helping and consoling, by orienting attention outward onto others and by reducing feelings of personal distress. (Smith, 2006; Singer and Klimecki, 2014) We have found diminished baseline RSA in bvFTD relates to reduced informant-reported agreeableness and lower prosocial behavior during laboratory-based tasks, deficits that both correlate with tissue loss in the left frontoinsula. (Sturm et al., 2018b; Sturm et al., 2017) Smaller gray matter volume in the bilateral medial pulvinar nucleus of the thalamus, a vulnerable region in *C9orf72* pathogenic expansion carriers, was also associated with diminished baseline RSA, prosocial behavior, and generosity in bvFTD. (Guo et al., 2016b; Sturm et al., 2018b).

In the present study, we examined basal parasympathetic activity and its relation to gray matter volume, behavioral symptom severity, and empathy in *C9orf72* pathogenic expansion carriers across the clinical continuum. We hypothesized that, like in sporadic bvFTD, baseline RSA would be impaired in people with FTD due to *C9orf72* pathogenic expansions but that lower baseline RSA levels might also be evident earlier in the disease course. Even decades prior to symptom onset, asymptomatic *C9orf72* pathogenic expansion carriers have weaker salience network connectivity (Lee et al., 2014) and lower informant-reported empathy than healthy family members who do not carry the mutation. (Foster et al., 2022; Gossink et al., 2022) To gain insights into when parasympathetic deficits manifest, we also assessed asymptomatic and mildly symptomatic *C9orf72* pathogenic expansion carriers with the expectation that baseline RSA impairments would be more pronounced in those with greater symptom severity. We next investigated where lower gray matter volume in the brain related to diminished baseline RSA across the *C9orf72* clinical spectrum. While some of the neural correlates of RSA deficits in *C9orf72*-mediated FTD may differ from those in sporadic cases, we expected much overlap with our prior studies. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) We hypothesized that in *C9orf72* pathogenic expansion carriers, lower baseline RSA would relate to smaller gray matter volume in the frontoinsula and medial pulvinar nucleus of the thalamus, early sites of dysfunction in *C9orf72* pathogenic expansion carriers, and to lower empathy.

## 2. Materials and methods

### 2.1. Participants

We enrolled 102 participants from the ARTFL LEFFTDs Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) project, a study that follows families with known or suspected familial FTD. All participants were evaluated at the University of California, San Francisco (UCSF) Memory and Aging Center. This study was approved by the Human Research Protection Program at the University of California, San Francisco, and all participants, or their surrogates, gave their informed

consent before participating.

Participants underwent an extensive multidisciplinary assessment that included a clinical interview, neurological exam, functional assessment, neuropsychological testing, and neuroimaging. The neuropsychological battery included tests of memory, language, executive functioning, visuospatial processing, and mood. (Kramer et al., 2003) The Frontotemporal Lobar Degeneration-Specific Clinical Dementia Rating scale (FTLD-CDR), which is based on a semi-structured interview with an informant, was used to assess behavioral symptom severity. (Knopman et al., 2008) Scores on the FTLD-CDR range from 0 (no symptoms) to 0.5 (very mild symptoms), 1 (mild symptoms), 2 (moderate symptoms), and 3 (severe symptoms).

Genetic testing confirmed that 49 participants in our sample had a *C9orf72* pathogenic repeat expansion ( $C9^+$ ). We used participants' clinical diagnoses and FTLD-CDR scores to determine their disease stage at the time of testing and to assign them to a clinical group. The  $C9^+$  group included healthy individuals without symptoms ( $C9^+$  asymp,  $n = 19$ ); those with mild cognitive impairment (MCI) or mild behavioral changes that did not interfere with functioning ( $C9^+$  MCI,  $n = 14$ ); and symptomatic individuals who met criteria for FTD ( $C9^+$  FTD,  $n = 16$ ). (Rascovsky et al., 2011) In the symptomatic group, nine met criteria for bvFTD, five had FTD and motor neuron disease (FTD-MND), one had semantic variant primary progressive aphasia, and one met no published research criteria yet exhibited executive deficits and disinhibition. The remaining 53 participants came from families with a known FTD-causing mutation but did not carry a pathogenic variant in the *C9orf72*, granulin precursor protein (*GRN*), or microtubule-associated protein tau (*MAPT*) genes. As the participants in this group did not carry the *C9orf72* pathogenic repeat expansion ( $C9^-$ ), and they were functionally intact (FTLD-CDR score of 0) and free of neurological and untreated psychiatric disorders, they served as the  $C9^-$  healthy control (HC) group (henceforth, " $C9^-$  HC").

To investigate our results in more detail, we included two additional comparison groups in subsequent analyses. Twenty-six participants with sporadic bvFTD (Rascovsky et al., 2011) (all were negative on genetic testing for *C9*; *MAPT*, and *GRN* mutations) and 25 older healthy controls (older HC) who were community-dwelling volunteers recruited from the Hillblom Healthy Aging Network, a longitudinal study of healthy aging at UCSF. These older HC, who were closer in age to the  $C9^+$  FTD group, completed the same clinical assessment as the other participants in the study. In addition to being cognitively normal and free of psychiatric and neurological disorders, all older HC had FTLD-CDR scores of zero. By including these additional groups in follow-up analyses, we were able to: (1) compare baseline RSA levels in  $C9^+$  FTD and sporadic FTD to assess whether there were comparable deficits were in both groups, and (2) confirm that baseline RSA deficits in  $C9^+$  FTD were still evident when compared to older HC instead of the younger  $C9^-$  HC group.

## 2.2. Procedure

Autonomic nervous system testing was conducted at the UCSF Center for Psychophysiology and Behavior. Prior to testing, height, and weight were recorded, and later used to compute measures of body mass index (BMI), which can influence RSA. (Masi et al., 2007; Maver et al., 2004; Arone et al., 1995) Participants also reported on their caffeine and tobacco use in the 24 h prior to the laboratory assessment. Their prescribed psychotropic medications psychotropic medications (i.e., benzodiazepine, dopamine agonist, serotonin antagonist and reuptake inhibitors, selective serotonin reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, and tricyclic antidepressants) were also recorded. Assessment of baseline autonomic activity, our focus here, was the first task in a larger battery of emotion-relevant tests that participants completed. These tasks and measures are not relevant to the present study.

## 2.3. Resting baseline task

Participants were seated in a comfortable chair in a well-lit experiment room and sat 4.25 feet away from a 21.4-inch computer monitor. Participants were asked to clear their minds and to look at a black "X" on a white background for two minutes.

## 2.4. Physiological recordings

Sensors were applied to participants to obtain continuous measures of physiological activity. Biopac MP150 bioamplifiers and a computer equipped with data acquisition software were used for all physiological data collection. Electrodes were placed in a bipolar configuration on opposite sides of the participant's chest to collect inter-beat interval (IBI) data. Inter-cycle interval (ICI) data was collected with pneumatic bellows or a respiration transducer that was stretched around the thoracic region. RSA was calculated as the difference in milliseconds between the shortest inter-beat interval during inspiration and the longest inter-beat interval during expiration. This "peak-valley" approach to RSA calculation provides an index of vagally-mediated parasympathetic activity. (Berntson et al., 1997; Grossman and Kollai, 1993).

Physiological data were processed using a custom pipeline, (Sturm et al., 2018b) scripted in AcqKnowledge software (v4.4, <https://www.biopac.com>). Four  $C9^+$  participants were tested but excluded from this study due to invalid physiological data (one participant had a sensor fail during testing, and three participants had cardiac arrhythmias for more than 10 percent of the baseline period).

## 2.5. Structural neuroimaging

Participants ( $n = 99$ ) underwent research-quality structural magnetic resonance imaging (MRI). Ninety-five percent of scans were collected within one week of the autonomic testing; in the remaining five percent, two  $C9^+$  participants had scans collected within three months of the autonomic testing, and three  $C9^-$  HC had scans collected within 12 months. Scans were completed on a 3 Tesla Siemens TIM Trio scanner equipped with a 12-channel head coil or a 3 Tesla Siemens Prisma scanner equipped with a 64-channel head coil both located at the UCSF Neuroscience Imaging Center. Whole brain structural images were acquired using volumetric 3D T1-weighted sagittal Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (160 sagittal slices; slice thickness = 1.0 mm; field-of-view [FOV] = 256 x 240 mm<sup>2</sup>; matrix 256 x 240; voxel size 1.0 x 1.0 x 1.0 mm<sup>3</sup>; repetition time [TR] = 2300 msec; TE=2.98 msec; flip angle = 9 degrees).

All structural MRI images were visually inspected for movement artifacts prior to being preprocessed in Statistical Parametric Mapping 12 (SPM12). (Penny et al., 2011) Structural images were segmented into gray matter using the segment program in SPM12 where images were modulated and warped to the Montreal Neurological Institute template. All other SPM12 default parameters were used. Segmented images were visually inspected for adequate segmentation and then smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

## 2.6. Informant-Reported empathy

Informants rated the  $C9^+$  participants current empathy levels on a short-form version of the Interpersonal Reactivity Index (IRI), a multi-dimensional measure of empathy (Davis, 1983) that is psychometrically valid in clinical and dementia populations. (Foster et al., 2022; Rankin et al., 2006) The Empathic Concern subscale measures the degree to which one helps and cares for others in need, a type of emotional empathy; the Perspective-Taking subscale measures the degree to which one can identify others' emotions and perspectives, a type of cognitive empathy. Each IRI subscale consists of seven items that are rated on 5-point Likert scales from 1 (*does not describe well*) to 5 (*describes well*).

Items were summed to calculate total subscale scores. Scores ranged from 7 to 35 with lower scores indicating lower empathy. IRI data were included if collected within six months of the autonomic assessment (95 % of participants had IRI measures completed by informants within a week of their autonomic testing). Seven C9<sup>+</sup> participants did not have available IRI data.

## 2.7. Statistical analysis

The statistical analyses were conducted in R Project (R Core Team, 2021) using RStudio. (RStudio Team, 2020) Analysis of variance (ANOVA) and chi-squared tests, where appropriate, were used to examine differences among the groups on the demographic, clinical, and neuropsychological measures.

We examined the distribution of baseline RSA and assessed the homogeneity of variance across the groups using Levene's test for equality of variances. As the baseline RSA data were skewed, and the groups had unequal variances,  $F=3.86$ ,  $p = 0.012$ , we conducted a natural log transformation of RSA, which improved the proximity to a normal distribution and resolved the issue with homogeneity of variance,  $F=1.82$ ,  $p = 0.149$ . An analysis of covariance (ANCOVA), controlling for age and sex, was used to test for group differences in baseline RSA. We also conducted several follow-up analyses in order to evaluate the robustness of our findings across the C9<sup>+</sup> spectrum with regard to age, medication use, and BMI. To compare baseline RSA in C9<sup>+</sup> FTD with that of sporadic bvFTD and older HC, we ran an additional ANCOVA (controlling for age and sex) in the C9<sup>-</sup> HC, older HC, C9<sup>+</sup> FTD, and sporadic bvFTD groups. Tukey-corrected *post hoc* tests were performed on all significant group effects to determine pairwise differences. In linear regression analyses, we examined whether lower baseline RSA predicted higher scores on the FTLD CDR Sum of Boxes and lower IRI empathy scores in the C9<sup>+</sup> participants when controlling for age and sex. Although we also investigated whether lower baseline RSA predicted lower scores on the Mini-Mental State Examination (MMSE), we did not expect an association given that MMSE is less sensitive to clinical severity in FTD. In all analyses, two-tailed tests were used with an alpha level of 0.05 to determine significance.

We conducted voxel-based morphometry (VBM) analyses with the voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003) toolbox in MATLAB. All analyses were masked to gray matter and included age, sex, total intracranial volume (to account for individual differences in head size), and scanner type as nuisance covariates. Whole-brain VBM analyses were performed to compare gray matter volume among the groups and to identify areas in which gray matter volume correlated with baseline RSA in the C9<sup>+</sup> participants ( $n = 47$ ). We also ran follow-up analyses of baseline RSA (same covariates as above) in the sporadic bvFTD group ( $n = 26$ ). To reduce Type 1 error resulting from multiple comparisons, permutation analyses were performed in VLSM. Statistical maps were calculated for 1,000 random assignments of the dependent variable, and the fifth percentile of the maximum cluster size was applied as a threshold to the raw  $p < 0.001$  map. This combined peak and extent threshold permutation-based method has been used in prior imaging studies using similar methods in related clinical groups. (Wilson et al., 2010; Sturm et al., 2013a; Shdo et al., 2022).

## 3. Results

### 3.1. Demographics and Neuropsychological Performance.

The groups did not differ in sex,  $X^2(3, N=102) = 3.44$ ,  $p = 0.328$ , or education,  $F(3, 96) = 0.94$ ,  $p = 0.426$ . Although the racial compositions of the groups were similar,  $X^2(15, N=94) = 9.60$ ,  $p = 0.844$ , the sample was predominantly White, which is consistent with the higher prevalence of C9orf72 pathogenic expansions in Europe and North America (Renton et al., 2011). As expected, there were group differences in age,  $F$

(3, 98) = 6.56,  $p < 0.001$ , such that the C9<sup>+</sup> FTD group was older than the C9<sup>-</sup> HC and C9<sup>+</sup> asymp groups. There were no differences in BMI,  $F(3, 90) = 1.02$ ,  $p = 0.389$ . The groups did not differ in their reported use of caffeine,  $X^2(3, N=101) = 3.67$ ,  $p = 0.300$ , or tobacco,  $X^2(3, N=102) = 5.64$ ,  $p = 0.131$ , in the 24 h prior to testing. They also did not differ in their prescribed medications,  $X^2(3, N=102) = 3.60$ ,  $p = 0.308$ .

On neuropsychological testing, the C9<sup>+</sup> FTD group had lower scores than the other groups on tests of visuospatial processing, semantic knowledge, and verbal episodic memory. The C9<sup>+</sup> MCI group had lower scores than both the C9<sup>-</sup> HC and C9<sup>+</sup> asymp groups on select tests of executive functioning and visual episodic memory. On a test of nonverbal generation, the C9<sup>+</sup> MCI group had lower scores than the C9<sup>-</sup> HC group but not the C9<sup>+</sup> asymp group. The C9<sup>+</sup> asymp group performed well on cognitive testing in general and did not differ from the C9<sup>-</sup> HC group on any cognitive measure. There were no group differences on the Geriatric Depression Scale, and scores were in the range of minimal depressive symptoms for all groups. See Table 1.

### 3.2. Baseline RSA is diminished in C9<sup>+</sup> FTD

An ANCOVA (controlling for age and sex) revealed a main effect of group on baseline RSA,  $F(3, 96) = 4.28$ ,  $p = 0.007$ . Tukey-corrected *post hoc* tests indicated that baseline RSA was lower in the C9<sup>+</sup> FTD group than in the C9<sup>-</sup> HC,  $t = -2.87$ ,  $p = 0.025$ ; C9<sup>+</sup> asymp,  $t = -3.33$ ,  $p = 0.006$ ; and C9<sup>+</sup> MCI,  $t = -2.83$ ,  $p = 0.028$ , groups. No other pairwise comparisons were significant (see Fig. 1a). The five individuals in the C9<sup>+</sup> FTD group with FTD-MND were not outliers in baseline RSA (their RSA levels fell within 2 standard deviations of the group mean). See Supplementary Fig. 1.

### 3.3. Follow-Up analyses

We conducted several follow-up analyses to test the robustness of our findings in people along the C9<sup>+</sup> clinical spectrum.

**Medications.** Twenty-six participants (11 C9<sup>-</sup> HC, 6 C9<sup>+</sup> asymp, 6 C9<sup>+</sup> MCI, and 3 C9<sup>+</sup> FTD) were prescribed beta blockers or psychotropic medications. First, we coded whether people were prescribed these medications (0 = no, 1 = yes) and added this variable as an additional covariate in our original analyses in the full sample. Controlling for medication use had little effect on our results: the main effect of group on baseline RSA persisted,  $F(3, 95) = 4.08$ ,  $p = 0.009$ , and the significant pairwise comparisons from the Tukey-corrected *post hoc* tests also remained unchanged. Next, we removed participants who were prescribed beta blockers or psychotropic medications from our full sample analysis, and our initial results endured. An ANCOVA revealed baseline RSA differences among the groups,  $F(3, 70) = 5.33$ ,  $p = 0.002$ , and the Tukey-corrected *post hoc* tests indicated the same significant pairwise differences.

**BMI.** In 94 participants with available data, we examined whether BMI related to our results. Consistent with prior studies, (Masi et al., 2007; Maver et al., 2004; Arone et al., 1995) higher BMI correlated with lower baseline RSA,  $r = -0.24$ ,  $t = -2.41$ ,  $p = 0.018$ , across the sample. When we added BMI as an additional covariate in our original analyses in the full sample, our main effect of group held,  $F(3, 87) = 3.60$ ,  $p = 0.017$ . While *post hoc* pairwise comparisons between the C9<sup>+</sup> FTD and C9<sup>-</sup> HC groups and the C9<sup>+</sup> FTD and C9<sup>+</sup> asymp groups remained significant, the comparison between C9<sup>+</sup> FTD and C9<sup>+</sup> MCI fell to trend level ( $p = 0.051$ ).

**Age.** Even in healthy populations, RSA is often lower in older adults than in younger adults, and heart rate variability can exhibit normal age-related decline. (De Meersman, 1993a; Lipsitz, 2002; Mulcahy et al., 2019; Uchino et al., 2010) Given that FTD symptoms become more likely with advancing age, we conducted additional tests to confirm that the baseline RSA deficits we detected in people with C9<sup>+</sup> FTD were not due to the older mean age of this group. To create an age-matched sample ( $n = 82$ ), we removed the youngest individuals from the C9<sup>-</sup> HC and C9<sup>+</sup>

**Table 1**  
Demographics and descriptive statistics.

|  | n   | C9 <sup>+</sup> HC                 | C9 <sup>+</sup> asymp              | C9 <sup>+</sup> MCI       | C9 <sup>+</sup> FTD                | Test Statistic  | p      |
|--|-----|------------------------------------|------------------------------------|---------------------------|------------------------------------|-----------------|--------|
| Age  | 102 | n = 53<br>46.5 (12.5) <sup>d</sup> | n = 19<br>43.9 (13.1) <sup>d</sup> | n = 14<br>53.9 (13.0)     | n = 16<br>59.3 (7.7) <sup>ab</sup> | F=6.56          | 0<.001 |
| Sex  | 102 |                                    |                                    |                           |                                    | $\chi^2 = 3.44$ | 0.328  |
| F  |     | 31 (58.5 %)                        | 10 (52.6 %)                        | 6 (42.9 %)                | 12 (75 %)                          |                 |        |
| M  |     | 22 (41.5 %)                        | 9 (47.4 %)                         | 8 (57.1 %)                | 4 (25 %)                           |                 |        |
| Race   | 94  |                                    |                                    |                           |                                    | $\chi^2 = 9.60$ | 0.844  |
| Asian Indian                                 |     | 1 (1.9 %)                          | 0 (0 %)                            | 0 (0 %)                   | 0 (0 %)                            |                 |        |
| Chinese                                      |     | 0 (0 %)                            | 0 (0 %)                            | 0 (0 %)                   | 1 (6.2 %)                          |                 |        |
| Filipino                                     |     | 1 (1.9 %)                          | 0 (0 %)                            | 0 (0 %)                   | 0 (0 %)                            |                 |        |
| Multiracial<br>(White + Native<br>American)  |     | 1 (1.9 %)                          | 0 (0 %)                            | 0 (0 %)                   | 0 (0 %)                            |                 |        |
| Multiracial<br>(White + not<br>specified)    |     | 1 (1.9 %)                          | 0 (0 %)                            | 0 (0 %)                   | 0 (0 %)                            |                 |        |
| White  |     | 42 (79.2 %)                        | 19 (100 %)                         | 14 (100 %)                | 14 (87.5 %)                        |                 |        |
| Did not specify                              |     | 7 (13.2 %)                         | 0 (0 %)                            | 0 (0 %)                   | 1 (6.2 %)                          |                 |        |
| Education                                    | 100 | 15.8 (2.5)                         | 16.3 (1.7)                         | 14.9 (2.1)                | 15.8 (2.6)                         | F=0.94          | 0.426  |
| Medications                                  | 102 |                                    |                                    |                           |                                    | $\chi^2 = 3.60$ | 0.308  |
| Yes  |     | 11 (20.8 %)                        | 6 (31.6 %)                         | 6 (42.9 %)                | 3 (18.8 %)                         |                 |        |
| No   |     | 42 (79.2 %)                        | 13 (68.4 %)                        | 8 (57.1 %)                | 13 (81.2 %)                        |                 |        |
| Body Mass Index                              | 94  | 28.0 (6.3)                         | 25.1 (4.8)                         | 27.9 (5.3)                | 27.6 (7.3)                         | F=1.02          | 0.389  |
| Caffeine Consumption                         | 101 |                                    |                                    |                           |                                    | $\chi^2 = 3.67$ | 0.300  |
| Yes  |     | 48 (90.6 %)                        | 15 (78.9 %)                        | 11 (78.6 %)               | 11 (73.3 %)                        |                 |        |
| No   |     | 5 (9.4 %)                          | 4 (21.1 %)                         | 3 (21.4 %)                | 4 (26.7 %)                         |                 |        |
| Tobacco Use                                  | 101 |                                    |                                    |                           |                                    | $\chi^2 = 5.64$ | 0.131  |
| Yes  |     | 8 (15.1 %)                         | 0 (0 %)                            | 2 (14.3 %)                | 0 (0 %)                            |                 |        |
| No   |     | 45 (84.9 %)                        | 19 (100 %)                         | 12 (85.7 %)               | 15 (100 %)                         |                 |        |
| Mini-Mental State Examination                | 93  | 28.7 (1.2) <sup>cd</sup>           | 28.5 (1.2) <sup>d</sup>            | 26.1 (2.6) <sup>ad</sup>  | 23.0 (6.2) <sup>abc</sup>          | F=7.28          | 0.001  |
| Modified Trails Errors                       | 93  | 0.2 (0.4)                          | 0.0 (0.0)                          | 1.2 (0.9)                 | 2.9 (3.4)                          | F=n/a           | n/a    |
| Modified Trails (# correct in 60 s)          | 93  | 42.7 (14.5) <sup>cd</sup>          | 46.2 (15.6) <sup>cd</sup>          | 22.4 (13.8) <sup>ab</sup> | 18.2 (15.0) <sup>ab</sup>          | F=16.6          | 0<.001 |
| Design Fluency Correct (# correct in 60 s)   | 93  | 12.7 (3.6) <sup>cd</sup>           | 11.2 (2.7) <sup>d</sup>            | 8.5 (2.8) <sup>a</sup>    | 6.8 (3.0) <sup>ab</sup>            | F=14.74         | 0<.001 |
| Design Fluency Repetitions                   | 93  | 1.8 (2.4)                          | 0.8 (1.3)                          | 0.8 (0.9)                 | 2.5 (2.3)                          | F=2.38          | 0.074  |
| Benson Figure Copy (/17)                     | 94  | 15.7 (0.6) <sup>d</sup>            | 15.8 (0.5) <sup>d</sup>            | 15.7 (0.7) <sup>d</sup>   | 14.4 (1.2) <sup>abc</sup>          | F=6.17          | 0.002  |
| Calculation                                  | 94  | 4.6 (0.6) <sup>d</sup>             | 4.7 (0.5) <sup>d</sup>             | 4.2 (0.7)                 | 3.5 (1.2) <sup>ab</sup>            | F=5.62          | 0.004  |
| Digits Backwards                             | 94  | 5.5 (1.4) <sup>cd</sup>            | 5.3 (1.0) <sup>cd</sup>            | 4.0 (1.1) <sup>ab</sup>   | 3.1 (1.5) <sup>ab</sup>            | F=15.37         | 0<.001 |
| Peabody Picture Vocabulary Test (/16)        | 94  | 15.5 (0.9) <sup>d</sup>            | 15.7 (0.5) <sup>d</sup>            | 15.0 (1.0) <sup>d</sup>   | 13.3 (2.6) <sup>abc</sup>          | F=5.88          | 0.003  |
| Phonemic Fluency (# correct in 60 s)         | 94  | 16.4 (5.1) <sup>d</sup>            | 15.2 (4.1) <sup>d</sup>            | 12.6 (5.5)                | 7.8 (6.0) <sup>ab</sup>            | F=11.03         | 0<.001 |
| Semantic Fluency (# correct in 60 s)         | 94  | 22.9 (5.6) <sup>cd</sup>           | 23.1 (4.6) <sup>cd</sup>           | 16.9 (3.1) <sup>ab</sup>  | 13.2 (6.9) <sup>ab</sup>           | F=14.74         | 0<.001 |
| Benson Figure Copy 10-Minute Recall (/17)    | 94  | 13.4 (2.3) <sup>cd</sup>           | 12.6 (2.1) <sup>cd</sup>           | 9.4 (3.3) <sup>ab</sup>   | 7.9 (5.0) <sup>ab</sup>            | F=9.6           | 0<.001 |
| Boston Naming Test Spontaneous Correct (/15) | 93  | 14.1 (1.2) <sup>d</sup>            | 13.9 (0.9) <sup>d</sup>            | 13.1 (1.9)                | 11.3 (3.7) <sup>ab</sup>           | F=3.49          | 0.029  |
| CVLT-MS: 10-Minute Delay Correct (/9)        | 89  | 7.8 (1.3) <sup>d</sup>             | 7.1 (1.9) <sup>d</sup>             | 6.3 (1.9) <sup>d</sup>    | 3.7 (3.1) <sup>abc</sup>           | F=9.15          | 0<.001 |
| Geriatric Depression Scale (/30)             | 86  | 5.2 (4.3)                          | 4.5 (6.0)                          | 5.7 (4.9)                 | 9.4 (6.8)                          | F=2.26          | 0.087  |

ANOVAs or chi-square tests, where appropriate, were used to compare the groups. Means (and standard deviations) are presented for the continuous variables; counts and within-group percentages are presented for the categorical variables. n/a = not applicable. Tukey-corrected *post hoc* tests were applied to significant ANOVAs: a = different from C9<sup>+</sup> HC, b = different from C9<sup>+</sup> asymp, c = different from C9<sup>+</sup> MCI, and d = different from C9<sup>+</sup> FTD at  $p < 0.05$ .

asymp groups (14 C9<sup>+</sup> HC group and 6 C9<sup>+</sup> asymp) until these groups no longer differed in age from the C9<sup>+</sup> FTD group (see [Supplementary Table 1](#)). Consistent with the results in the full sample, an ANCOVA (controlling for age and sex) in the age-matched sample yielded a main effect of group on baseline RSA,  $F(3, 76) = 4.23, p = 0.008$ . Tukey-corrected *post hoc* tests revealed the same significant pairwise comparisons as in the full sample (see [Fig. 1b](#)).

**Additional Group Comparisons.** To confirm that the baseline RSA deficits in the sporadic bvFTD and the C9<sup>+</sup> FTD groups were similar and that they persisted when RSA in these groups was contrasted with the older HC as well as the younger C9<sup>+</sup> HC, we conducted an ANCOVA (controlling for age and sex) that compared baseline RSA among the C9<sup>+</sup> HC, older HC, C9<sup>+</sup> FTD, and sporadic bvFTD groups. The groups were similar in sex, education, and race, and they had similar cognitive profiles on neuropsychological testing. Although the older HC group was older than the C9<sup>+</sup> HC and C9<sup>+</sup> FTD groups, their mean age did not differ from the sporadic bvFTD group. Likewise, the C9<sup>+</sup> FTD and sporadic bvFTD groups were both older than the C9<sup>+</sup> HC group but did not differ from each other. See [Supplementary Table 2](#).

The ANCOVA revealed a main effect of group on baseline RSA,  $F(3, 114) = 8.93, p < 0.001$ . Tukey-corrected *post hoc* tests indicated that both the C9<sup>+</sup> FTD group,  $t = -3.05, p = 0.015$ , and the sporadic bvFTD group,  $t = -2.64, p = 0.045$ , had lower baseline RSA than the C9<sup>+</sup> HC

group. The C9<sup>+</sup> FTD group,  $t = -4.00, p < 0.001$ , and the sporadic bvFTD group,  $t = -3.89, p < 0.001$ , also had lower baseline RSA than the older HC group. As expected, the C9<sup>+</sup> FTD and sporadic bvFTD groups did not differ from each other,  $t = 0.62, p = 0.925$ . Baseline RSA in the C9<sup>+</sup> HC and older HC groups also did not differ,  $t = 1.22, p = 0.613$ . See [Supplementary Fig. 2](#).

### 3.4. Lower baseline RSA predicts greater behavioral symptom severity and lower empathy in C9<sup>+</sup> participants

A linear regression analysis in the C9<sup>+</sup> group found that lower baseline RSA predicted higher FTL DCD Sum of Boxes scores,  $\beta = -0.43, t(45) = -2.65, p = 0.011$ , but not lower MMSE,  $\beta = 0.30, t(41) = 1.61, p = 0.116$  (see [Fig. 2](#)). In the C9<sup>+</sup> participants, lower baseline RSA also predicted lower scores on both empathic concern,  $\beta = 0.63, t(38) = 3.16, p = 0.003$ , and perspective taking,  $\beta = 0.46, t(38) = 2.25, p = 0.032$ , subscales of the IRI ([Fig. 3](#)). The individuals in the C9<sup>+</sup> FTD group with FTD-MND were not outliers in empathic concern or perspective taking (their levels fell within 2 standard deviations of the group mean) and did not drive the associations found across the C9<sup>+</sup> clinical spectrum. See [Supplementary Fig. 3](#).

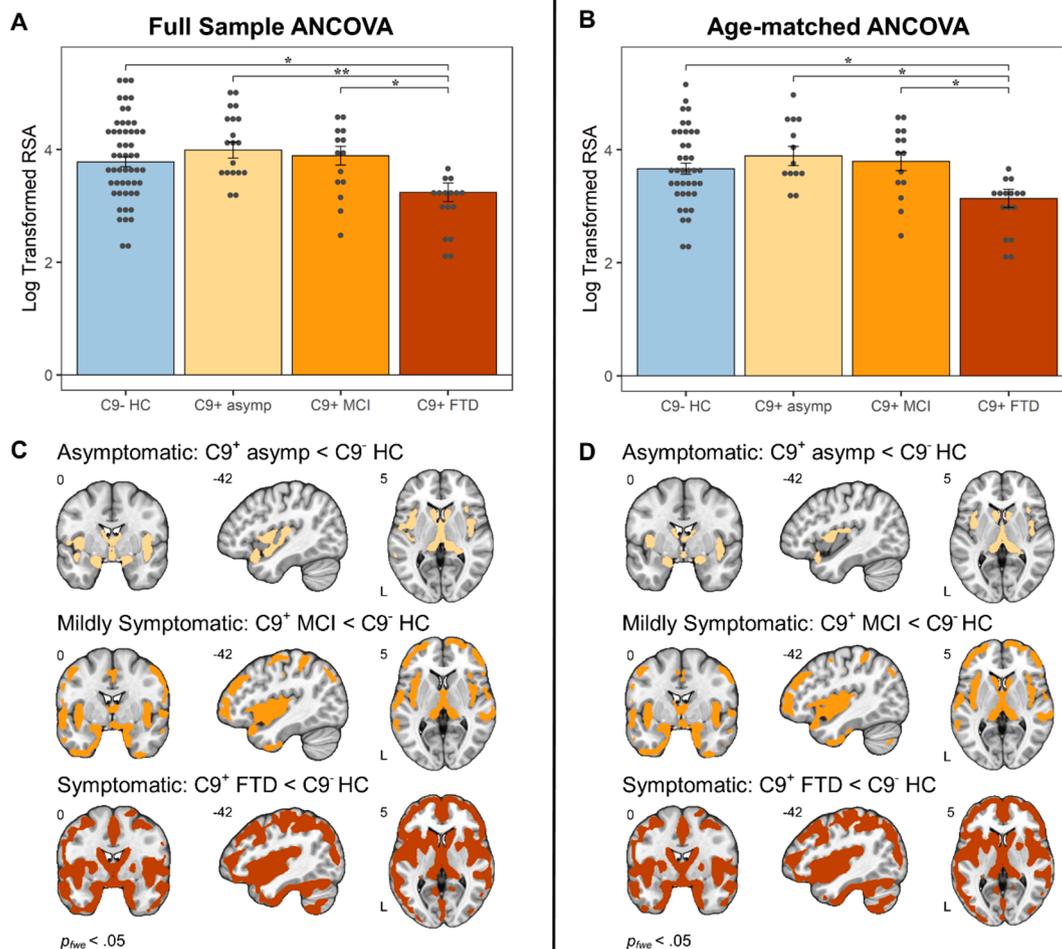


Fig. 1. Baseline respiratory sinus arrhythmia levels and gray matter maps in the *C9orf72* pathogenic expansion carriers.

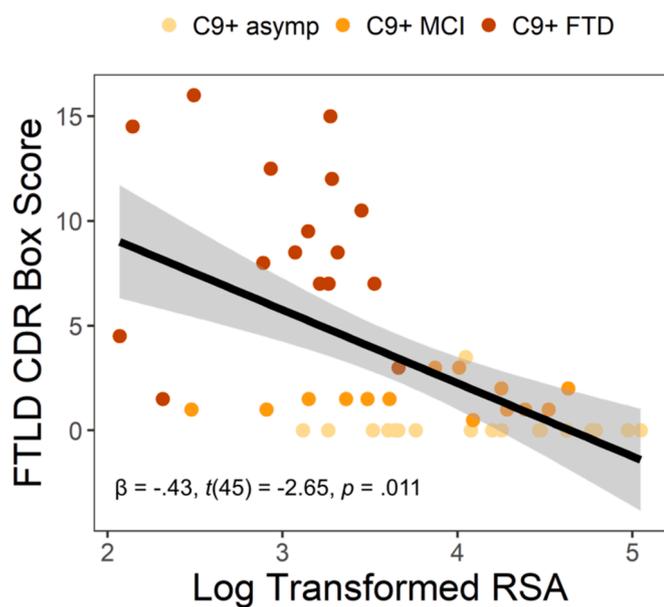


Fig. 2. Greater disease severity related to lower baseline respiratory sinus arrhythmia in *C9orf72* pathogenic expansion carriers.

3.5. Smaller gray matter volume in *C9+* participants at each stage of behavioral symptom severity

Consistent with prior studies, (Sha et al., 2012; Mahoney et al., 2012a; Whitwell et al., 2012; Yokoyama and Rosen, 2012; Heuer et al., 2020) whole-brain neuroimaging analyses found smaller gray matter volume in the frontal and temporal lobes as well as in the insula, thalamus, parietal lobes, cingulate cortex, operculum, basal ganglia, and cerebellum in the *C9+* FTD group than in the *C9* HC (see Supplementary Table 3). Compared to the other *C9+* groups, the atrophy in the *C9+* FTD group was the most severe and distributed. While the *C9+* MCI and *C9+* asymp participants also had smaller gray matter volume in the insula, thalamus, operculum, and basal ganglia than the *C9* HC, only in the *C9+* MCI participants did these differences extend to the frontal lobes, parietal lobes, cingulate cortex, temporal lobes, and cerebellum, which is consistent with previous studies (Lee et al., 2017; Cash et al., 2018). See Fig. 1c and Supplementary Table 3. In the age-matched sample, the gray matter topographies of each group were consistent with those seen in the full sample (see Fig. 1d).

3.6. Lower baseline RSA correlates with smaller left frontoinsula and bilateral thalamus volume across the *C9+* clinical spectrum

Whole-brain neuroimaging analyses in the *C9+* participants revealed that lower baseline RSA correlated with smaller gray matter volume in the left frontoinsula, bilateral thalamus (including bilateral medial pulvinar nuclei), cerebellum (including the cerebellum VI and vermis VI), and occipital lobe,  $p_{FWE} < 0.05$  (see Table 2 and Fig. 4A). There were

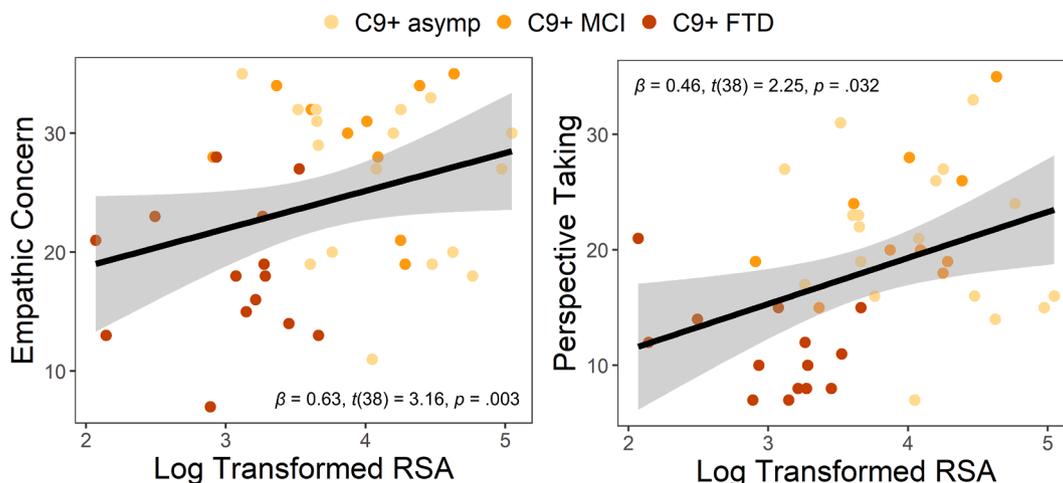


Fig. 3. Lower baseline RSA predicted lower empathy in the *C9orf72* pathogenic expansion carriers.

Table 2

Regions in which smaller gray matter volume related to lower baseline RSA in the *C9+* group.

| Anatomical Region             | Cluster Extent (mm <sup>3</sup> ) | Peak MNI Coordinates |     |     | Maximum <i>T</i> |
|-------------------------------|-----------------------------------|----------------------|-----|-----|------------------|
|                               |                                   | x                    | y   | z   |                  |
| Occipital Middle, L           | 29,736                            | -32                  | -87 | 32  | 6.31             |
| Thalamus, Bilateral           | —                                 | —                    | —   | —   | —                |
| Cerebellum, Bilateral         | —                                 | —                    | —   | —   | —                |
| Rectus, L                     | 1912                              | -3                   | 29  | -27 | 4.33             |
| Frontal Medial Orbital, L     | —                                 | —                    | —   | —   | —                |
| Rectus, R                     | —                                 | —                    | —   | —   | —                |
| Frontal Inferior Orbital 2, L | 1547                              | -53                  | 23  | -11 | 4.41             |
| Frontoinsula, L               | —                                 | —                    | —   | —   | —                |
| Frontal Middle 2, R           | 726                               | 50                   | 21  | 36  | 5.07             |

All clusters presented survived 1000 permutations at a cut off cluster size with an  $\alpha = 0.05$ . Regions were labeled using the AAL2 atlas. x, y, and z = Montreal Neurological Institute (MNI) coordinates in the left–right, anterior-posterior, and inferior-superior dimensions, respectively. All contrasts are positive (smaller gray matter volume related to lower RSA).

no regions at this threshold in which lower baseline RSA related to larger gray matter volume. To ensure that the VBM correlations were not accounted for by extreme values in any of the clinical groups, we extracted the gray matter volume in the two clusters with the strongest associations with baseline RSA. Scatterplots confirmed baseline RSA had a linear association with volume in the left frontoinsula cluster (see

Fig. 4B) and the occipitoparietal – thalamus cluster (Supplementary Fig. 4) across the *C9+* clinical spectrum. The same neuroimaging analyses in the sporadic bvFTD group revealed no significant clusters at this statistical threshold.

#### 4. Discussion

The findings of the present study indicate that, like in sporadic bvFTD, baseline parasympathetic activity is impaired in FTD due to *C9orf72* pathogenic expansions. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) In *C9+* participants, baseline RSA deficits were more notable in those with FTD than in those who were asymptomatic or with very mild symptoms and were comparable to deficits found in sporadic bvFTD. These results were robust and held when accounting for various potential confounding factors including age, sex, beta-blocker and psychotropic medication prescription, and BMI. RSA deficits were also substantially lower when compared to the older HC sample, further supporting the disease-specific effects on parasympathetic decline. Although the asymptomatic *C9+* participants did not differ from the mildly symptomatic *C9+* participants or the *C9+* healthy controls in the pairwise comparisons, the means fell in a pattern suggestive of gradual decline. Linear regressions across the *C9+* clinical spectrum found additional evidence for more pronounced baseline RSA impairment with disease progression as participants with lower baseline RSA had greater behavioral symptom severity (as measured by the FTLCDR Sum of Boxes) and lower empathy. Lower baseline RSA was not associated with greater cognitive impairment (as measured by the MMSE), however,

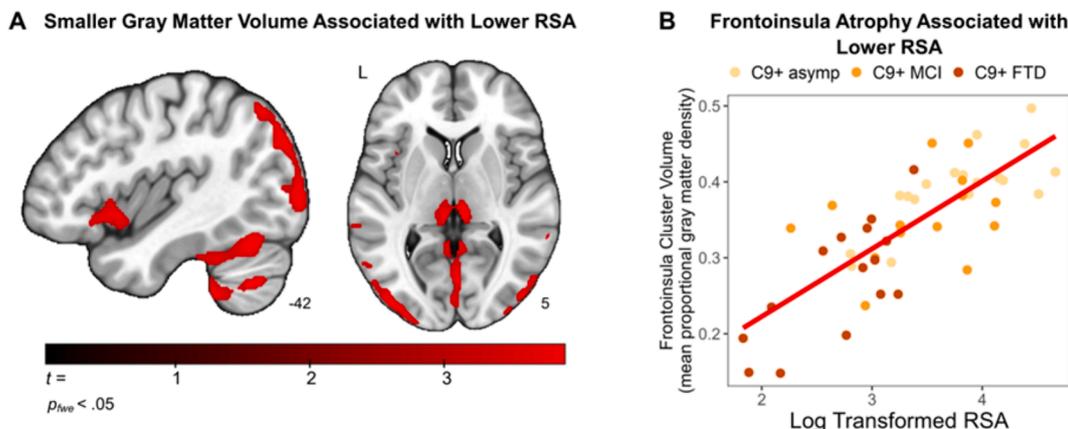


Fig. 4. Smaller gray matter volume related to lower baseline respiratory sinus arrhythmia in *C9orf72* pathogenic expansion carriers.

which suggests RSA deficits may have a stronger association with behavioral decline. Whole-brain structural neuroimaging analyses across the  $C9^+$  clinical spectrum revealed lower baseline RSA related to smaller gray matter volume in the left frontoinsula and bilateral thalamus, parietal lobe, occipital lobe, and cerebellum, regions that are important for parasympathetic function and vulnerable in  $C9orf72$  pathogenic expansion carriers.

Our previous research has uncovered baseline RSA impairments in bvFTD that relate to degeneration and dysfunction in brain regions that support parasympathetic control. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) While our prior studies examined samples that included sporadic and genetic cases of bvFTD, here we clarify that basal parasympathetic activity is diminished in both sporadic bvFTD and in FTD due to  $C9orf72$  pathogenic expansions. The neural correlates of baseline RSA deficits in  $C9^+$  participants resemble those found in bvFTD and highlight the central role of the left frontoinsula in parasympathetic control. Considered a final waystation in central parasympathetic networks, the left frontoinsula receives afferent information from the viscera that first passes through the brainstem, (Sturm et al., 2018a; Seeley et al., 2012) thalamus, posterior insula, and mid-insula. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b; Beauchaine, 2001; Porges, 2001; Thayer and Lane, 2000; Decety, 2015; Decety, 2011; Craig, 2002; Critchley and Harrison, 2013) In  $C9^+$  participants, smaller gray matter volume in the bilateral thalamus (including the medial pulvinar nucleus), parietal cortex, occipital cortex, and cerebellum was also related to lower baseline RSA. Although occipital and parietal cortices are not typically associated with RSA, the cerebellum plays a role in parasympathetic activity (Beissner et al., 2013; Gianaros et al., 2004; Muhtadie et al., 2014) and empathy (Adamaszek et al., 2017; Singer et al., 2004) through its connections with the frontoinsula and anterior cingulate cortex. (Guo et al., 2016a) Disruption of these pathways in  $C9orf72$  pathogenic expansions may impede transmission of internal signals that are critical for parasympathetic functioning and associated socioemotional processes.

The parasympathetic nervous system promotes empathy and prosocial behavior by fostering shared feeling states and emotional understanding. (Porges, 2001) In our prior research, we found lower baseline RSA in bvFTD predicted diminished prosocial behavior during a laboratory-based task in which participants witnessed an experimenter struggling to find a lost key. (Sturm et al., 2018b) The results of the present study suggest that waning parasympathetic activity may also underlie the lower empathy levels that characterize the asymptomatic and symptomatic phases of  $C9orf72$ -mediated disease. (Lee et al., 2014; Foster et al., 2022) Years before functional impairment, asymptomatic  $C9orf72$  pathogenic expansion carriers have reduced empathy (Foster et al., 2022) in addition to lower functional connectivity (Lee et al., 2017; Lee et al., 2014; Foster et al., 2022) and smaller gray matter volume (Yokoyama and Rosen, 2012; Agosta et al., 2017; Sha et al., 2012; Lee et al., 2017; Lee et al., 2014; Cash et al., 2018; Whitwell et al., 2007) in the medial pulvinar nucleus of the thalamus, an area in which atrophy relates to diminished prosocial behavior in FTD. (Sturm et al., 2018b; Sturm et al., 2017) Although it remains to be determined when the parasympathetic nervous system begins to falter in  $C9orf72$  pathogenic expansion carriers, we found some evidence for baseline RSA disruption early in the clinical course when symptoms are very mild. We speculate that parasympathetic decline may contribute to the emergence and progression of behavioral symptoms in  $C9orf72$  pathogenic expansion carriers by reducing their access to physiological cues that typically shape emotional experience and encourage empathy. (Miller et al., 2016; Sassenrath et al., 2021; Hastings and Miller, 2014; Palser et al., 2021).

Recent years have brought rapid advances in FTD biomarker development, and baseline RSA may be useful for monitoring in the early stages of the disease. Although fluid biomarkers (e.g., poly-GP and neurofilament light chain levels) measured from cerebrospinal fluid show promise for tracking symptom imminence and disease progression

in  $C9orf72$  pathogenic expansions and other forms of FTD, (Meeter et al., 2018; Cajanus et al., 2020; Wilke et al., 2022) noninvasive biomarkers in FTD are still lacking. Given the central role that the parasympathetic system plays in social behavior and empathy, RSA may be a potential new biomarker that is sensitive to behavioral symptom progression in FTD. Consistent with this possibility, we found a strong linear association between baseline RSA and FTLD CDR Sum of Boxes scores, but not MMSE, in  $C9^+$  participants across the clinical spectrum. While our results suggest there may be a gradual decline in baseline RSA over time, it is also possible that RSA remains relatively stable until symptoms emerge. As disease onset can be difficult to determine in  $C9orf72$  pathogenic expansion carriers (Sha et al., 2012; Mahoney et al., 2012a; Devenney et al., 2014; Snowden et al., 2012; Kertesz et al., 2013)—with some people exhibiting psychiatric symptoms in the initial stages of the illness, (Takada and Sha, 2012) and others showing a slow clinical progression (Khan et al., 2012)—additional research is necessary to determine the temporal trajectory of RSA decline throughout the disease course and to elucidate how parasympathetic deficits relate to other biomarkers and pathological changes such as aggregation of FTLD-TDP, dipeptide repeat protein inclusions, and RNA foci. (Meeter et al., 2018; Vatsavayai et al., 2016) A better understanding of the pathophysiological cascade and its relation to parasympathetic dysfunction may not only be relevant to FTD due to  $C9orf72$  pathogenic expansions but may also shed light on the biological mechanisms underlying sporadic disease.

There are limitations to this research to consider. First, this study was cross-sectional, and we did not have longitudinal autonomic and neuroimaging data available in our sample. As the asymptomatic and very mildly symptomatic  $C9^+$  participants varied in age and proximity to symptom onset, (Rohrer et al., 2015; Gijssels et al., 2016; Glasmacher et al., 2020) baseline RSA may have varied widely even within each clinical group. Studies that measure baseline RSA over time in  $C9orf72$  pathogenic expansion carriers will be needed to determine how parasympathetic changes relate to within-subject clinical progression. Second, we focused on the structural neuroanatomical correlates of baseline RSA deficits in  $C9^+$  participants, but functional connectivity neuroimaging studies would also help to shed light on how neural network dysfunction relates to parasympathetic impairment. In  $C9orf72$  pathogenic expansion carriers, deficits in functional connectivity may precede atrophy and, thus, may be more sensitive to early disruption. (Lee et al., 2017) Network-based analyses will be important for elucidating how salience network hypoconnectivity might underlie baseline RSA deficits in  $C9orf72$  pathogenic expansion carriers. Third, there are numerous other potential confounding variables that could influence RSA that we did not assess in the present study. For example, sleep plays a crucial role in the modulation of autonomic activity, and prior work has shown that sleep deprivation can influence autonomic regulation and health of the cardiovascular system. (Takase et al., 2004; Bourdillon et al., 2021; Krause et al., 2017) Exercise, in contrast, may increase vagal tone. (Stein et al., 1999; De Meersman, 1993b; Sandercock et al., 2005) Although BMI did not significantly impact our findings, we did not directly assess physical activity or level of fitness in the participants. We also did not assess recent recreational drug use, which could have affected baseline RSA levels. Fourth, our study focused on  $C9^+$  participants, which may limit the generalizability of our findings to sporadic FTD or to FTD due to other genetic causes. Whether parasympathetic deficits are also present in other familial forms of FTD will be an important topic for future research.

This study provides novel evidence that basal parasympathetic activity is diminished in FTD due to a  $C9orf72$  pathogenic expansion, much like it is impaired in sporadic bvFTD. Baseline RSA deficits were more pronounced in individuals with more severe behavioral symptoms and related to smaller gray matter volume in brain regions that support parasympathetic function and to lower empathy. Overall, our findings suggest autonomic measures offer a new avenue for biomarker development in genetic forms of FTD where the prediction of symptom onset

is critical as disease-modifying therapies are on the horizon.

## Funding

This study was supported by grants R01AG052496, R01AG058233, P01AG019724, and U19AG063911 from the NIA National Institute on Aging and NIH National Institutes of Health; and The Larry L. Hillblom Foundation (2013-A-029-SUP and 2005/2T).

## CRediT authorship contribution statement

**Ashlin R. K. Roy:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fate Noohi:** Writing – review & editing. **Nathaniel A. Morris:** Writing – review & editing, Resources, Investigation. **Peter Ljubenkov:** Resources. **Hilary Heuer:** Resources, Data curation. **Jamie Fong:** Resources, Data curation. **Matthew Hall:** Resources, Data curation. **Argentina Lario Lago:** Resources, Data curation. **Katherine P. Rankin:** Writing – review & editing, Resources. **Bruce L. Miller:** Writing – review & editing, Funding acquisition. **Adam L. Boxer:** Resources. **Howard J. Rosen:** Resources, Funding acquisition. **William W. Seeley:** Writing – review & editing, Supervision. **David C. Perry:** Writing – review & editing, Supervision. **Jennifer S. Yokoyama:** Writing – review & editing, Supervision. **Suzee E. Lee:** Writing – review & editing, Supervision, Funding acquisition. **Virginia E. Sturm:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2024.103649>.

## References

- Adamaszek, M., D'Agata, F., Ferrucci, R., et al., 2017. Consensus Paper: Cerebellum and Emotion. *The Cerebellum*. 16 (2), 552–576. <https://doi.org/10.1007/s12311-016-0815-8>.
- Agosta, F., Ferraro, P.M., Riva, N., et al., 2017. Structural and functional brain signatures of C9orf72 in motor neuron disease. *Neurobiol Aging*. 57, 206–219. <https://doi.org/10.1016/j.neurobiolaging.2017.05.024>.
- Arone, L.J., Mackintosh, R., Rosenbaum, M., Leibel, R.L., Hirsch, J., 1995. Autonomic nervous system activity in weight gain and weight loss. *Am. J. Physiol.-Regul Integr. Comp. Physiol.* 269 (1), R222–R225. <https://doi.org/10.1152/ajpregu.1995.269.1.R222>.
- Bang, J., Spina, S., Miller, B.L., 2015. Frontotemporal dementia. *The Lancet*. 386 (10004), 1672–1682. [https://doi.org/10.1016/S0140-6736\(15\)00461-4](https://doi.org/10.1016/S0140-6736(15)00461-4).
- Barker, M.S., Gottesman, R.T., Manooch, M., et al., March 10, 2022. Proposed research criteria for prodromal behavioural variant frontotemporal dementia. *Brain*. Published Online awab365. <https://doi.org/10.1093/brain/awab365>.
- Bates, E., Wilson, S.M., Saygin, A.P., et al., 2003. Voxel-based lesion–symptom mapping. *Nat Neurosci*. 6 (5), 448–450. <https://doi.org/10.1038/nn1050>.
- Batson, C.D., Batson, J.G., Todd, R.M., Brummett, B.H., Shaw, L.L., Aldeguer, C.M.R., 1995. Empathy and the collective good: Caring for one of the others in a social dilemma. *J. Pers. Soc. Psychol.* 68, 619–631. <https://doi.org/10.1037/0022-3514.68.4.619>.
- Beauchaine, T., 2001. Vagal tone, development, and Gray's motivational theory: toward an integrated model of autonomic nervous system functioning in psychopathology. *Dev Psychopathol.* 13 (2), 183–214. <https://doi.org/10.1017/S0954579401002012>.
- Beauchaine, T.P., Gatzke-Kopp, L., Neuhaus, E., Chipman, J., Reid, M.J., Webster-Stratton, C., 2013. Sympathetic- and parasympathetic-linked cardiac function and prediction of externalizing behavior, emotion regulation, and prosocial behavior among preschoolers treated for ADHD. *J. Consult. Clin. Psychol.* 81 (3), 481–493. <https://doi.org/10.1037/a0032302>.
- Beissner, F., Meissner, K., Bär, K.J., Napadow, V., 2013. The autonomic brain: an activation likelihood estimation meta-analysis for central processing of autonomic function. *J. Neurosci.* 33 (25), 10503. <https://doi.org/10.1523/JNEUROSCI.1103-13.2013>.
- Berntson, G.G., Cacioppo, J.T., Quigley, K.S., 1993. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. *Psychophysiology*. 30 (2), 183–196. <https://doi.org/10.1111/j.1469-8986.1993.tb01731.x>.
- Berntson GG, Thomas Bigger Jr. J, Eckberg DL, et al. Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology*. 1997;34(6):623-648. Doi: 10.1111/j.1469-8986.1997.tb02140.x.
- Bertrand, A., Wen, J., Rinaldi, D., et al., 2018. Early cognitive, structural, and microstructural changes in presymptomatic C9orf72 carriers younger than 40 years. *JAMA Neurol.* 75 (2), 236–245. <https://doi.org/10.1001/jamaneurol.2017.4266>.
- Bocchetta, M., Iglesias, J.E., Neason, M., Cash, D.M., Warren, J.D., Rohrer, J.D., 2020. Thalamic nuclei in frontotemporal dementia: Mediodorsal nucleus involvement is universal but pulvinar atrophy is unique to C9orf72. *Hum Brain Mapp.* 41 (4), 1006–1016. <https://doi.org/10.1002/hbm.24856>.
- Boeve, B.F., Boylan, K.B., Graff-Radford, N.R., et al., 2012. Characterization of frontotemporal dementia and/or amyotrophic lateral sclerosis associated with the GGGGCC repeat expansion in C9ORF72. *Brain*. 135 (3), 765–783. <https://doi.org/10.1093/brain/aww004>.
- Bonham LW, Geier EG, Sirkis DW, et al. Radiogenomics of <em>C9orf72</em> expansion carriers reveals global transposable element de-repression and enables prediction of thalamic atrophy and clinical impairment. *bioRxiv*. Published online January 1, 2022:2022.07.28.501897. Doi: 10.1101/2022.07.28.501897.
- Bourdillon, N., Jeanneret, F., Nilchian, M., Albertoni, P., Ha, P., Millet, G.P., 2021. Sleep Deprivation Deteriorates Heart Rate Variability and Photoplethysmography. *Front Neurosci.* 15. <https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2021.642548>.
- Cajanus, A., Katsisko, K., Kontkanen, A., et al., 2020. Serum neurofilament light chain in FTL: association with C9orf72, clinical phenotype, and prognosis. *Ann Clin Transl Neurol.* 7 (6), 903–910. <https://doi.org/10.1002/actn.3.51041>.
- Cash, D.M., Bocchetta, M., Thomas, D.L., et al., 2018. Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study. *Neurobiol Aging*. 62, 191–196. <https://doi.org/10.1016/j.neurobiolaging.2017.10.008>.
- Convery, R., Mead, S., Rohrer, J.D., 2019. Review: Clinical, genetic and neuroimaging features of frontotemporal dementia. *Neuropathol Appl Neurobiol.* 45 (1), 6–18. <https://doi.org/10.1111/nan.12535>.
- Craig, A.D., 2002. How do you feel? interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci.* 3 (8), 655–666. <https://doi.org/10.1038/nrn894>.
- Craig, A.D. (Bud), 2005. Forebrain emotional asymmetry: a neuroanatomical basis? *Trends Cogn. Sci.* 9 (12), 566–571. <https://doi.org/10.1016/j.tics.2005.10.005>.
- Critchley, H.D., Harrison, N.A., 2013. Visceral influences on brain and behavior. *Neuron*. 77 (4), 624–638. <https://doi.org/10.1016/j.neuron.2013.02.008>.
- Davis, M.H., 1983. Measuring individual differences in empathy: Evidence for a multidimensional approach. *J. Pers. Soc. Psychol.* 44 (1), 113–126. <https://doi.org/10.1037/0022-3514.44.1.113>.
- De Meersman, R.E., 1993a. Aging as a modulator of respiratory sinus arrhythmia. *J Gerontol.* 48 (2), B74–B78. <https://doi.org/10.1093/geronj/48.2.B74>.
- De Meersman, R.E., 1993b. Heart rate variability and aerobic fitness. *Am Heart J*. 125 (3), 726–731. [https://doi.org/10.1016/0002-8703\(93\)90164-5](https://doi.org/10.1016/0002-8703(93)90164-5).
- Decety, J., 2011. Dissecting the Neural Mechanisms Mediating Empathy. *Emot. Rev.* 3 (1), 92–108. <https://doi.org/10.1177/1754073910374662>.
- Decety, J., 2015. The neural pathways, development and functions of empathy. *Soc. Behav.* 3, 1–6. <https://doi.org/10.1016/j.cobeha.2014.12.001>.
- DeJesus-Hernandez, M., Mackenzie, I.R., Boeve, B.F., et al., 2011. Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. *Neuron*. 72 (2), 245–256. <https://doi.org/10.1016/j.neuron.2011.09.011>.
- Devenney, E., Hornberger, M., Irish, M., et al., 2014. Frontotemporal Dementia Associated With the C9ORF72 Mutation: A Unique Clinical Profile. *JAMA Neurol.* 71 (3), 331–339. <https://doi.org/10.1001/jamaneurol.2013.6002>.
- Di Bello, M., Carnevali, L., Petrocchi, N., Thayer, J.F., Gilbert, P., Ottaviani, C., 2020. The compassionate vagus: a meta-analysis on the connection between compassion and heart rate variability. *Neurosci. Biobehav. Rev.* 116, 21–30. <https://doi.org/10.1016/j.neubiorev.2020.06.016>.
- Eckart, J.A., Sturm, V.E., Miller, B.L., Levenson, R.W., 2012. Diminished disgust reactivity in behavioral variant frontotemporal dementia. *Neuropsychologia*. 50 (5), 786–790. <https://doi.org/10.1016/j.neuropsychologia.2012.01.012>.
- Foster PH, Russell LL, Peakman G, et al. Examining empathy deficits across familial forms of frontotemporal dementia within the GENFI cohort. *Cortex*. Published online February 9, 2022. 10.1016/j.cortex.2022.01.012.
- Gendron, T.F., Chew, J., Stankowski, J.N., et al., 2017. Poly(GP) proteins are a useful pharmacodynamic marker for C9ORF72-associated amyotrophic lateral sclerosis. *Sci Transl Med.* 9(383):eaai7866 <https://doi.org/10.1126/scitranslmed.aai7866>.
- Gianaros, P.J., Van der Veen, F.M., Jennings, J.R., 2004. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: Implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology*. 41 (4), 521–530. <https://doi.org/10.1111/1469-8986.2004.00179.x>.

- Gijssels, I., Van Langenhove, T., van der Zee, J., et al., 2012. A C9orf72 promoter repeat expansion in a Flanders-Belgian cohort with disorders of the frontotemporal lobar degeneration-amyotrophic lateral sclerosis spectrum: a gene identification study. *Lancet Neurol.* 11 (1), 54–65. [https://doi.org/10.1016/S1474-4422\(11\)70261-7](https://doi.org/10.1016/S1474-4422(11)70261-7).
- Gijssels, I., Van Mossevelde, S., van der Zee, J., et al., 2016. The C9orf72 repeat size correlates with onset age of disease, DNA methylation and transcriptional downregulation of the promoter. *Mol Psychiatry.* 21 (8), 1112–1124. <https://doi.org/10.1038/mp.2015.159>.
- Glasmacher, S.A., Wong, C., Pearson, I.E., Pal, S., 2020. Survival and prognostic factors in C9orf72 repeat expansion carriers: a systematic review and meta-analysis. *JAMA Neurol.* 77 (3), 367–376. <https://doi.org/10.1001/jamaneurol.2019.3924>.
- Goetz, J.L., Keltner, D., Simon-Thomas, E., 2010. Compassion: an evolutionary analysis and empirical review. *Psychol. Bull.* 136 (3), 351–374. <https://doi.org/10.1037/a0018807>.
- Flora Gossink, Annemiek Dols, Max L Stek, et al. Early life involvement in C9orf72 repeat expansion carriers. *J. Neurol. Neurosurg. Amp. Psychiatry.* 2022;93(1):93. 10.1136/jnnp-2020-325994.
- Greaves, C.V., Rohrer, J.D., 2019. An update on genetic frontotemporal dementia. *J Neurol.* 266 (8), 2075–2086. <https://doi.org/10.1007/s00415-019-09363-4>.
- Grossman, P., Kolli, M., 1993. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: Within- and between-individual relations. *Psychophysiology.* 30 (5), 486–495. <https://doi.org/10.1111/j.1469-8986.1993.tb02072.x>.
- Guo, C.C., Tan, R., Hodges, J.R., Hu, X., Sami, S., Hornberger, M., 2016a. Network-selective vulnerability of the human cerebellum to Alzheimer's disease and frontotemporal dementia. *Brain.* 139 (5), 1527–1538. <https://doi.org/10.1093/brain/aww003>.
- Guo, C.C., Sturm, V.E., Zhou, J., et al., 2016b. Dominant hemisphere lateralization of cortical parasympathetic control as revealed by frontotemporal dementia. *Proc Natl Acad Sci.* 113 (17), E2430. <https://doi.org/10.1073/pnas.1509184113>.
- Hastings PD, Miller JG. Autonomic regulation, polyvagal theory, and children's prosocial development. In: *Prosocial Development: A Multidimensional Approach*. Oxford University Press; 2014:112-127. 10.1093/acprof:oso/9780199964772.003.0006.
- Heuer, H.W., Wang, P., Rascovsky, K., et al., 2020. Comparison of sporadic and familial behavioral variant frontotemporal dementia (FTD) in a North American cohort. *Alzheimers Dement.* 16 (1), 60–70. <https://doi.org/10.1002/alz.12046>.
- Hua, A.Y., Chen, K.H., Brown, C.L., et al., 2019. Physiological, behavioral and subjective sadness reactivity in frontotemporal dementia subtypes. *Soc. Cogn. Affect. Neurosci.* 14 (12), 1453–1465. <https://doi.org/10.1093/scan/nsaa007>.
- Joshi, A., Mendez, M.F., Kaiser, N., Jimenez, E., Mather, M., Shapira, J.S., 2014. Skin conductance levels may reflect emotional blunting in behavioral variant frontotemporal dementia. *J. Neuropsychiatry Clin. Neurosci.* 26 (3), 227–232. <https://doi.org/10.1176/appi.neuropsych.12110332>.
- Kertesz, A., Ang, L.C., Jesso, S., et al., 2013. Psychosis and hallucinations in frontotemporal dementia with the C9ORF72 mutation: a detailed clinical cohort. *Cogn Behav Neurol.* 26 (3), 146–154.
- Khan, B.K., Yokoyama, J.S., Takada, L.T., et al., 2012. Atypical, slowly progressive behavioral variant frontotemporal dementia associated with <em>C9ORF72</em> hexanucleotide expansion. *J Neurol Neurosurg Amp Psychiatry.* 83 (4), 358. <https://doi.org/10.1136/jnnp-2011-301883>.
- Knopman, D.S., Kramer, J.H., Boeve, B.F., et al., 2008. Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain.* 131 (11), 2957–2968. <https://doi.org/10.1093/brain/awn234>.
- Kogan, A., Oveis, C., Carr, E., et al., 2015. Vagal activity is quadratically related to prosocial traits, prosocial emotions, and observer perceptions of prosociality. *J Pers Soc Psychol.* 107 <https://doi.org/10.1037/a0037509>.
- Kramer, J.H., Jurik, J., Sha, S.J., et al., 2003. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cogn. Behav. Neurol.* 16 (4). [https://journals.lww.com/cogbehavneurol/Fulltext/2003/12000/Distinctive\\_Neuropsychological\\_Patterns\\_in.2.aspx](https://journals.lww.com/cogbehavneurol/Fulltext/2003/12000/Distinctive_Neuropsychological_Patterns_in.2.aspx).
- Krause, A.J., Simon, E.B., Mander, B.A., et al., 2017. The sleep-deprived human brain. *Nat. Rev. Neurosci.* 18 (7), 404–418. <https://doi.org/10.1038/nrn.2017.55>.
- Kiril, J.J., Macdonald, V., Patel, S., Png, F., Halliday, G.M., 2005. Distribution of brain atrophy in behavioral variant frontotemporal dementia. *J Neurol Sci.* 232 (1), 83–90. <https://doi.org/10.1016/j.jns.2005.02.003>.
- Lee, S.E., Khazenzon, A.M., Trujillo, A.J., et al., 2014. Altered network connectivity in frontotemporal dementia with C9orf72 hexanucleotide repeat expansion. *Brain.* 137 (11), 3047–3060. <https://doi.org/10.1093/brain/awu248>.
- Lee, S.E., Sias, A.C., Mandelli, M.L., et al., 2017. Network degeneration and dysfunction in presymptomatic C9ORF72 expansion carriers. *NeuroImage Clin.* 14, 286–297. <https://doi.org/10.1016/j.nicl.2016.12.006>.
- Lehmer, C., Oeckl, P., Weishaup, J.H., et al., 2017. Poly-GP in cerebrospinal fluid links C9orf72-associated dipeptide repeat expression to the asymptomatic phase of ALS/FTD. *EMBO Mol Med.* 9 (7), 859–868. <https://doi.org/10.15252/emmm.201607486>.
- Ling, S.C., Polymenidou, M., Cleveland, D.W., 2013. Converging Mechanisms in ALS and FTD: Disrupted RNA and Protein Homeostasis. *Neuron.* 79 (3), 416–438. <https://doi.org/10.1016/j.neuron.2013.07.033>.
- Lipsitz, L.A., 2002. Dynamics of stability: the physiologic basis of functional health and frailty. *J. Gerontol. Ser. A.* 57 (3), B115–B125. <https://doi.org/10.1093/gerona/57.3.B115>.
- Mahoney, C.J., Beck, J., Rohrer, J.D., et al., 2012a. Frontotemporal dementia with the C9ORF72 hexanucleotide repeat expansion: clinical, neuroanatomical and neuropathological features. *Brain.* 135 (3), 736–750. <https://doi.org/10.1093/brain/awr361>.
- Mahoney, C.J., Downey, L.E., Ridgway, G.R., et al., 2012b. Longitudinal neuroimaging and neuropsychological profiles of frontotemporal dementia with C9ORF72 expansions. *Alzheimers Res Ther.* 4 (5), 41. <https://doi.org/10.1186/alzrt144>.
- Majounie, E., Renton, A.E., Mok, K., et al., 2012. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.* 11 (4), 323–330. [https://doi.org/10.1016/S1474-4422\(12\)70043-1](https://doi.org/10.1016/S1474-4422(12)70043-1).
- Marshall, C.R., Hardy, C.J.D., Russell, L.L., et al., 2019. The functional neuroanatomy of emotion processing in frontotemporal dementias. *Brain.* 142 (9), 2873–2887. <https://doi.org/10.1093/brain/awz204>.
- Masi, C.M., Hawkey, L.C., Rickett, E.M., Cacioppo, J.T., 2007. Respiratory sinus arrhythmia and diseases of aging: Obesity, diabetes mellitus, and hypertension. *Spec Issue Biol. Psychol. Card Vagal Control Emot. Psychopathol. Health.* 74 (2), 212–223. <https://doi.org/10.1016/j.biopsycho.2006.07.006>.
- Maver, J., Strucl, M., Accetto, R., 2004. Autonomic nervous system and microvascular alterations in normotensives with a family history of hypertension. *Blood Press.* 13 (2), 95–100. <https://doi.org/10.1080/08037050310031035>.
- Meeter, L.H.H., Gendron, T.F., Sias, A.C., et al., 2018. Poly(GP), neurofilament and grey matter deficits in C9orf72 expansion carriers. *Ann Clin Transl Neurol.* 5 (5), 583–597. <https://doi.org/10.1002/acn3.559>.
- Miller, J.G., Nuselovici, J.N., Hastings, P.D., 2016. Nonrandom acts of kindness: parasympathetic and subjective empathic responses to sadness predict children's prosociality. *Child Dev.* 87 (6), 1679–1690. <https://doi.org/10.1111/cdev.12629>.
- Moore, K.M., Nicholas, J., Grossman, M., et al., 2019. Age at symptom onset and death and disease duration in genetic frontotemporal dementia: an international retrospective cohort study. *Lancet Neurol.* 19 (2), 145–156. [https://doi.org/10.1016/S1474-4422\(19\)30394-1](https://doi.org/10.1016/S1474-4422(19)30394-1).
- Muhtadie L, Koslov K, Akinola M, Mendes W. Vagal Flexibility: a physiological predictor of social sensitivity. *J Pers Soc Psychol.* Published online July 1, 2014. 10.1037/pspp0000016.
- Muhtadie, L., Haase, C.M., Verstaen, A., Sturm, V.E., Miller, B.L., Levenson, R.W., 2019. Neuroanatomy of expressive suppression: The role of the insula. *Emotion.* 21 (2), 405–418. <https://doi.org/10.1037/emo0000710>.
- Mulcahy, J.S., Larsson, D.E.O., Garfinkel, S.N., Critchley, H.D., 2019. Heart rate variability as a biomarker in health and affective disorders: A perspective on neuroimaging studies. *NeuroImage.* 202, 116072 <https://doi.org/10.1016/j.neuroimage.2019.116072>.
- Oveis, C., Cohen, A.B., Gruber, J., Shiot, M.N., Haidt, J., Keltner, D., 2009. Resting respiratory sinus arrhythmia is associated with tonic positive emotionality. *Emotion.* 9, 265–270. <https://doi.org/10.1037/a0015383>.
- Palsler, E.R., Morris, N.A., Roy, A.R.K., et al., 2021. Children with developmental dyslexia show elevated parasympathetic nervous system activity at rest and greater cardiac deceleration during an empathy task. *Biol Psychol.* 166, 108203 <https://doi.org/10.1016/j.biopsycho.2021.108203>.
- Pan, P., Song, W., Yang, J., et al., 2012. Gray matter atrophy in behavioral variant frontotemporal dementia: a meta-analysis of voxel-based morphometry studies. *Dement Geriatr Cogn Disord.* 33 (2–3), 141–148. <https://doi.org/10.1159/000338176>.
- Penny, W.D., Friston, K.J., Ashburner, J.T., Kiebel, S.J., Nichols, T.E., 2011. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*. Elsevier.
- Porges, S.W., 2001. The polyvagal theory: phylogenetic substrates of a social nervous system. *Int. J. Psychophysiol.* 42 (2), 123–146. [https://doi.org/10.1016/S0167-8760\(01\)00162-3](https://doi.org/10.1016/S0167-8760(01)00162-3).
- Porges, S.W., 2003. The polyvagal theory: phylogenetic contributions to social behavior. *Tribute Paul MacLean Neurobiol. Relev. Soc. Behav.* 79 (3), 503–513. [https://doi.org/10.1016/S0031-9384\(03\)00156-2](https://doi.org/10.1016/S0031-9384(03)00156-2).
- Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. *Cleve Clin. J. Med.* 2009;76 Suppl 2(Suppl 2):S86-90. 10.3949/ccjm.76.s2.17.
- R Core Team. R: A Language and Environment for Statistical Computing. Published online 2021. <https://www.R-project.org/>.
- Rankin, K.P., Gorno-Tempini, M.L., Allison, S.C., et al., 2006. Structural anatomy of empathy in neurodegenerative disease. *Brain.* 129 (11), 2945–2956. <https://doi.org/10.1093/brain/awl254>.
- Rascovsky, K., Hodges, J.R., Knopman, D., et al., 2011. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* 134 (9), 2456–2477. <https://doi.org/10.1093/brain/awr179>.
- Renton, A.E., Majounie, E., Waite, A., et al., 2011. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-Linked ALS-FTD. *Neuron.* 72 (2), 257–268. <https://doi.org/10.1016/j.neuron.2011.09.010>.
- Rohrer, J.D., Isaacs, A.M., Mizielinska, S., et al., 2015. C9orf72 expansions in frontotemporal dementia and amyotrophic lateral sclerosis. *Lancet Neurol.* 14 (3), 291–301. [https://doi.org/10.1016/S1474-4422\(14\)70233-9](https://doi.org/10.1016/S1474-4422(14)70233-9).
- Rosen, H.J., Gorno-Tempini, M.L., Goldman, W.P., et al., 2002. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology.* 58 (2), 198. <https://doi.org/10.1212/WNL.58.2.198>.
- RStudio Team. RStudio: Integrated Development for R. RStudio. Published online 2020. <http://www.rstudio.com/>.
- Sandercock, G.R.H., Bromley, P.D., Brodie, D.A., 2005. Effects of exercise on heart rate variability: inferences from meta-analysis. *Med. Sci. Sports Exerc.* 37 (3), 433–439. <https://doi.org/10.1249/01.mss.0000155388.39002.9d>.
- Sassenrath, C., Barthelmäs, M., Saur, J., Keller, J., 2021. Inducing empathy affects cardiovascular reactivity reflected in changes in high-frequency heart rate variability. *Cogn. Emot.* 35 (2), 393–399. <https://doi.org/10.1080/02699931.2020.1826910>.

- Scherling, C.S., Zakrzewski, J., Datta, S., et al., 2017. Mistakes, too few to mention? Impaired self-conscious emotional processing of errors in the behavioral variant of frontotemporal dementia. *Front. Behav. Neurosci.* 11, 189. <https://doi.org/10.3389/fnbeh.2017.00189>.
- Seeley, W.W., Menon, V., Schatzberg, A.F., et al., 2007. Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J. Neurosci.* 27 (9), 2349. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>.
- Seeley, W.W., Crawford, R., Rascovsky, K., et al., 2008. Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch. Neurol.* 65 (2), 249–255. <https://doi.org/10.1001/archneurol.2007.38>.
- Seeley, W.W., Zhou, J., Kim, E.J., 2012. Frontotemporal dementia: what can the behavioral variant teach us about human brain organization? *The Neuroscientist.* 18 (4), 373–385. <https://doi.org/10.1177/1073858411410354>.
- Sha, S.J., Takada, L.T., Rankin, K.P., et al., 2012. Frontotemporal dementia due to C9ORF72 mutations: Clinical and imaging features. *Neurology.* 79 (10), 1002. <https://doi.org/10.1212/WNL.0b013e318268452e>.
- Shdo, S.M., Roy, A.R.K., Datta, S., et al., 2022. Enhanced positive emotional reactivity in frontotemporal dementia reflects left-lateralized atrophy in the temporal and frontal lobes. *Cortex.* 154, 405–420. <https://doi.org/10.1016/j.cortex.2022.02.018>.
- Singer, T., Klimecki, O.M., 2014. Empathy and compassion. *Curr. Biol.* 24 (18), R875–R878. <https://doi.org/10.1016/j.cub.2014.06.054>.
- Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., Frith, C.D., 2004. Empathy for Pain Involves the Affective but not Sensory Components of Pain. *Science.* 303 (5661), 1157–1162. <https://doi.org/10.1126/science.1093535>.
- Smith, A., 2006. Cognitive empathy and emotional empathy in human behavior and evolution. *Psychol. Rec.* 56 (1), 3–21. <https://doi.org/10.1007/BF03395534>.
- Snowden, J.S., Rollinson, S., Thompson, J.C., et al., 2012. Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. *Brain.* 135 (3), 693–708. <https://doi.org/10.1093/brain/awr355>.
- Solje, E., Aaltokallio, H., Koivumaa-Honkanen, H., et al., 2015. The Phenotype of the C9ORF72 Expansion Carriers According to Revised Criteria for bvFTD. *PLOS ONE.* 10 (7), e0131817.
- Stein, P.K., Ehsani, A.A., Domitrovich, P.P., Kleiger, R.E., Rottman, J.N., 1999. Effect of exercise training on heart rate variability in healthy older adults. *Am Heart J.* 138 (3), 567–576. [https://doi.org/10.1016/S0002-8703\(99\)70162-6](https://doi.org/10.1016/S0002-8703(99)70162-6).
- Stellar, J.E., Cohen, A., Oveis, C., Keltner, D., 2015. Affective and physiological responses to the suffering of others: compassion and vagal activity. *J. Pers. Soc. Psychol.* 108 (4), 572–585. <https://doi.org/10.1037/pspi0000010>.
- Sturm, V.E., Rosen, H.J., Allison, S., Miller, B.L., Levenson, R.W., 2006. Self-conscious emotion deficits in frontotemporal lobar degeneration. *Brain.* 129 (9), 2508–2516. <https://doi.org/10.1093/brain/awl145>.
- Sturm, V.E., Ascher, E.A., Miller, B.L., Levenson, R.W., 2008. Diminished self-conscious emotional responding in frontotemporal lobar degeneration patients. *Emotion.* 8 (6), 861–869. <https://doi.org/10.1037/a0013765>.
- Sturm, V.E., Yokoyama, J.S., Seeley, W.W., Kramer, J.H., Miller, B.L., Rankin, K.P., 2013a. Heightened emotional contagion in mild cognitive impairment and Alzheimer's disease is associated with temporal lobe degeneration. *Proc. Natl. Acad. Sci. U.S.A.* 110 (24), 9944–9949. <https://doi.org/10.1073/PNAS.1301119110>.
- Sturm, V.E., Sollberger, M., Seeley, W.W., et al., 2013b. Role of right pregenual anterior cingulate cortex in self-conscious emotional reactivity. *Soc. Cogn. Affect. Neurosci.* 4 (4), 468–474. <https://doi.org/10.1093/scan/nss023>.
- Sturm, V.E., Perry, D.C., Wood, K., et al., 2017. Prosocial deficits in behavioral variant frontotemporal dementia relate to reward network atrophy. *Brain Behav.* 7 (10), e00807.
- Sturm, V.E., Brown, J.A., Hua, A.Y., et al., 2018a. Network architecture underlying basal autonomic outflow: evidence from frontotemporal dementia. *J. Neurosci.* 38 (42), 8943. <https://doi.org/10.1523/JNEUROSCI.0347-18.2018>.
- Sturm, V.E., Sible, I.J., Datta, S., et al., 2018b. Resting parasympathetic dysfunction predicts prosocial helping deficits in behavioral variant frontotemporal dementia. *Cortex.* 109, 141–155. <https://doi.org/10.1016/j.cortex.2018.09.006>.
- Takada, L.T., Sha, S.J., 2012. Neuropsychiatric features of C9orf72-associated behavioral variant frontotemporal dementia and frontotemporal dementia with motor neuron disease. *Alzheimers Res Ther.* 4 (5), 38. <https://doi.org/10.1186/alzrt141>.
- Takase, B., Akima, T., Satomura, K., et al. Effects of chronic sleep deprivation on autonomic activity by examining heart rate variability, plasma catecholamine, and intracellular magnesium levels. *4th Int Symp Workshop Circadian Rhythms Clin Chronother.* 2004; 58:S35-S39. 10.1016/S0753-3322(04)80007-6.
- Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. *Arousal Anxiety.* 61 (3), 201–216. [https://doi.org/10.1016/S0165-0327\(00\)00338-4](https://doi.org/10.1016/S0165-0327(00)00338-4).
- Uchino, B.N., Birmingham, W., Berg, C.A., 2010. Are older adults less or more physiologically reactive? a meta-analysis of age-related differences in cardiovascular reactivity to laboratory tasks. *J. Gerontol Ser B.* 65B (2), 154–162. <https://doi.org/10.1093/geronb/gbp127>.
- Vatsavayai, S.C., Yoon, S.J., Gardner, R.C., et al., 2016. Timing and significance of pathological features in C9orf72 expansion-associated frontotemporal dementia. *Brain.* 139 (12), 3202–3216. <https://doi.org/10.1093/brain/aww250>.
- Vatsavayai, S.C., Nana, A.L., Yokoyama, J.S., Seeley, W.W., 2019. C9orf72-FTD/ALS pathogenesis: evidence from human neuropathological studies. *Acta Neuropathol (Berl).* 137 (1), 1–26. <https://doi.org/10.1007/s00401-018-1921-0>.
- Verstaen, A., Eckart, J.A., Muhtadie, L., et al., 2016. Insular atrophy and diminished disgust reactivity. *Emotion.* 16 (6) <https://doi.org/10.1037/emo0000195>.
- Whitwell, J.L., Sampson, E.L., Loy, C.T., et al., 2007. VBM signatures of abnormal eating behaviours in frontotemporal lobar degeneration. *NeuroImage.* 35 (1), 207–213. <https://doi.org/10.1016/j.neuroimage.2006.12.006>.
- Whitwell, J.L., Weigand, S.D., Boeve, B.F., et al., 2012. Neuroimaging signatures of frontotemporal dementia genetics: C9ORF72, tau, progranulin and sporadics. *Brain.* 135 (3), 794–806. <https://doi.org/10.1093/brain/aww001>.
- Wilke, C., Reich, S., van Swieten, J.C., et al., 2022. Stratifying the Presymptomatic Phase of Genetic Frontotemporal Dementia by Serum NFL and pNfH: A Longitudinal Multicentre Study. *Ann Neurol.* 91 (1), 33–47. <https://doi.org/10.1002/ana.26265>.
- Wilson, S.M., Henry, M.L., Besbris, M., et al., 2010. Connected speech production in three variants of primary progressive aphasia. *Brain.* 133 (7), 2069–2088. <https://doi.org/10.1093/brain/awq129>.
- Yokoyama, J.S., Rosen, H.J., 2012. Neuroimaging features of C9ORF72 expansion. *Alzheimers Res Ther.* 4 (6), 45. <https://doi.org/10.1186/alzrt148>.
- Zhou, J., Greicius, M.D., Gennatas, E.D., et al., 2010. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. *Brain.* 133 (5), 1352–1367. <https://doi.org/10.1093/brain/awq075>.